REMARKS

Claim 1 has been amended to recite that the upper limit of the amount of parabens is 1.125 mg/ml, and new claim 27 has been added wherein the upper limit is 1 mg/ml (as previously in claim 1). Support for these amendments can be found on page 4, lines 27-30.

Rejection of claims 1-2, 5, 12, and 17 under 35 USC 103

Claims 1-2, 5, 12, and 17 were rejected as obvious over DeLongueville et al. (WO 02/47689 A2), Gilliland 1 (1992; J. Appl. Bacteriol.; 72: 252-57); and Gilliland 2 (1992; J. Appl. Bacteriol.; 72:258-61) in view of Routledge (1998; Toxicol. Appl. Pharmacol.; 153:12-19).

In the previous Office Action response, the applicants noted that Doron et al (2001; Int. J. Antimicrob. Agents; 18: 575-78) taught the lowest total concentration of the combination of MP and PP to be completely antibacterial is 1.55 mg/ml for liquid, planktonic bacterial growth. The examiner agreed that it would have been nonobvious to reduce the concentrations of parabens to less than 1.55 mg/ml, let alone by more than 35%, down to 1 mg/ml, as the applicants had argued. One of ordinary skill in the art would have avoided using smaller concentrations (i.e., below 1.5 mg/ml, which includes the upper limit of 1.125 mg/ml of amended claim 1 and new claim 27) because they would believe or reasonably expect that such concentrations (as presently claimed) would render a composition susceptible to bacterial growth. The instant rejection suffers similarly.

Gilliland 1 presents a study of the effect of temperature on the kill rate of *E. coli* by methyl and propyl parabens, providing kinetic data produced from experiments using mixtures of 0.12% w/v methylparaben and 0.012% w/v propylparaben, i.e. at a 10:1 [MP]:[PB] ratio. The total paraben concentration was 0.132% for all reported experiments. The kinetic study revealed first order kill kinetics. No data was presented for total paraben concentrations under 0.132%. The applicants note that the present claims recite total paraben concentration of < 1 mg/ml (0.1 % w/v).

Furthermore, the temperatures tested by Gilliland 1 were between 34 °C and 42 °C (page 254, col. 1), which is well outside the temperature range pharmaceuticals such as recited in the present claims are stored. And, the test was only one inoculation of the medium with *E. coli*, not a continuous inoculation with bacteria and fungi.

In view of the foregoing, nothing in Gilliland 1 would have given one of ordinary skill in the art reason make the presently claimed compositions or to expect the bactericidal results achieved.

Gilliland 2 presents a similar study using four different mixtures of methylparaben and propylparaben. The experiments also employed elevated temperatures (37 °C) for measurement of kill kinetics, and, so, like Gilliland 1, its teachings would have been recognized as of limited value for a pharmaceutical composition such as presently claimed.

But even to the extent that its teachings are applicable, they would *dissuade* the ordinary artisan from the presently claimed composition.

As noted, Gilliland 2 studied kill kinetics of four mixtures of parabens (Table 1, page 259):

(a) 0.12 % methylparaben and 0.012% propylparaben:,
- total paraben 0.132%
- [MB]:[PB] = 10:1

(b) 0.12 % methylparaben and 0.014% propylparaben:
- total paraben 0.136%
- [MB]:[PB] = 8.6:1

(c) 0.14 % methylparaben and 0.012% propylparaben:
- total paraben 0.152%
- [MB]:[PB] = 11.7:1

(d) 0.14 % methylparaben and 0.014% propylparaben:
- total paraben 0.154%
- [MB]:[PB] = 10:1

Gilliland 2 teaches that methylparaben at 0.12% or 0.14% when used alone was bacteriostatic, but not bacteriacidal, And propylparaben at 0.012% or 0.014% when used alone allowed bacterial growth. (page 260, first full paragraph). Gilliland 2 teaches that concentrations below (a) – (d) were not studied because "at lower concentrations the combinations were often only bacteriostatic and consistent kill rate constants could not be calculated." (page 259, fourth paragraph).

The measured rate constant as a function of methylparaben concentration is presented in Fig. 2 of Gilliland 2 (rate constants obtained from Table 1 of Gilliland 2):

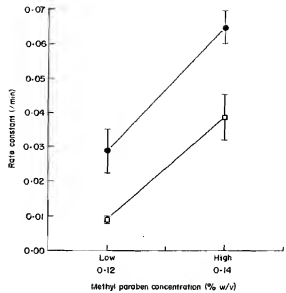

Fig. 2 Results of factorial design experiment to evaluate the effect of methyl and propyl paraben combinations on the kill rate constant of *Escherichia coli*. (Error bars are s.e., $n = 20$.) □, Low propyl paraben; ●, high propyl paraben

- The y-axis is placed at a methylparaben concentration of approximately 0.11%.
  - Positive y-value rate constants correspond to microbial kill.
  - Negative y-value rate constants correspond to microbial growth.

The total concentration of parabens at which there is no bactericidal effect can be readily calculated for [MP]:[PB] = 10:1 by extrapolating the line defined by points (d) and (a) (both having [MP]:[PB] = 10:1) to a rate constant of 0. That line is calculable as follows:

$$\text{slope} = \frac{0.0649 - 0.0091}{0.14 - 0.12} = 2.79$$

and

$$\text{intercept} = \text{rate} - \text{slope} \cdot [\text{MB}] = 0.0649 - 2.79 \cdot 0.14 = -0.3257,$$

yielding the linear equation:

$$\text{rate} = 2.79 \cdot [\text{MB}] - 0.3257.$$

Thus, the rate goes to zero (i.e., the solution loses its bactericidal activity) at

$$[\text{MB}] = \frac{0.3257}{2.79} = 0.1167 \text{ w/v\%}.$$

So, for the ratio [MP]:[PB] = 10:1, the total paraben concentration at which bactericidal activity vanishes is

[MB] + [PB] = (0.1167) + 0.1 (0.1167) = 0.1283 w/v % = 1.283 mg/ml.

And while this is for a ratio [MB]:[PB]=10:1 rather than the claimed 9:1, this clearly suggests that total concentrations below 1 mg/ml for a ratio of 9:1 would be expected not to be bactericidal at this temperature, thus teaching away from the present claims.

Routledge teaches that the GRAS level for parabens is 0.1% w/w. The FDA establishes GRAS (Generally Recognized As Safe) levels for food additives. 27 CFR §170. The agency establishes the level, typically using a 100:1 margin of safety. 27 CFR §170.22. Thus, the GRAS designation and level for parabens is unrelated to the effectiveness of parabens as antimicrobial agents. A principal advantage of being at or under permitted GRAS levels is that the use of the material will not require the food manufacturer to obtain additional pre-market notification review by the FDA under 27 CFR §170.100. Regardless, the FDA routinely subjects pharmaceutical compositions to pre-approval reviews, 21 CFR §314.105(c), so the advantage of coming in under the GRAS level is minimal.

Indeed, as stated in Routledge (page 16, right, 3rd paragraph), maximum levels of parabens in pharmaceutical products seldom exceed 1% w/w, while the Danish cosmetic regulations permit a maximum combined concentration of 0.8% w/w (both levels far exceeding GRAS levels), implying that exceeding GRAS levels is permissible. As an example, the assignee of the present application, UCB Pharma, recently launched an oral solution of a drug effective in the treatment of epilepsy diseases, which solution contains more than 2.5 mg/ml of paraben, greatly exceeding the GRAS level.

Those of ordinary skill in the art recognize that for a liquid pharmaceutical composition to be safe, useful, and achieve regulatory approval, a complete antibacterial effect must be achieved. Furthermore, the antibacterial efficacy of a pharmaceutical composition must be continuously maintained over long periods of time and multiple potential exposures to bacteria. While liquid pharmaceutical formulations are manufactured to be bacteria-free and sealed, they may be repeatedly exposed to the risk of bacterial contamination each time the container is opened (such as with drops). And acceptable pharmaceutical formulation must be completely bacterial resistant under such circumstances throughout the life of the product (21 CFR §314.125(b).

Thus, in balancing the antibacterial requirements against any perceived advantage in achieving GRAS standards, one or ordinary skill in the art would have essentially ignored

Routledge's teachings concerning GRAS in view of Gilliland 2's suggestion that such levels of methyl and propyl parabens would fail to be bactericidal.

In summary, the applicants respectfully submit that one of ordinary skill in the art could not have predicted or had a reasonable expectation that a liquid levocetirizine-containing solution would be completely antibacterial with concentrations of the combination of methyl- and propylparabens of less than 1 mg/ml because,

1. The lowest completely antibacterial concentration of the combination of MP + PP disclosed by Gilliland 1 and Gilliland 2 is > 1.3 mg/ml, with lower concentrations stated to be bacteriostatic and not bactericidal.
2. The contour plot from the 2^2 factorial designed experiment of Gilliland 2 teaches that at total paraben concentrations under about 1.2 mg/ml the preservative mixtures will be ineffective.
3. Routledge teaches that while levels of parabens should be kept at a minimum, both the FDA and Danish authorities recognize that patient safety allows parabens at levels exceeding about 8 – 10 mg/g.

It is therefore unexpected and nonobvious that compositions according to the claims would have antibacterial efficacy observed. The unexpected efficacy of the claimed compositions is manifested in Tables 15-20 of Example 4 of the present application, which show that levocetirizine compositions according to claim 1 with total paraben concentrations ([MP] + [PP]) of from 0.375 mg/ml up to 1.125 mg/ml (and [MP]:[PP] = 9) are free of *Pseudomonas aeruginosa*, *E. coli,* and *Staphylococcus aureus* bacteria 14 and 28 days following inoculation with these bacteria, respectively.[1]

In view of the foregoing, the applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

[1] *Candida albicans* and *Aspergillus niger* are fungi.

If there are any questions or comments regarding this application, the Examiner is encouraged to contact the undersigned in order to expedite prosecution.

Respectfully submitted,

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